PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FPAA570PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IN2005/000019	International filing date *(day/month/year)* 17.01.2005	Priority date *(day/month/year)* 19.01.2004
International Patent Classification (IPC) or national classification and IPC INV. C07D209/52		
Applicant LUPIN LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.11.2005	27.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Deutsch, W Telephone No. +49 89 2399-8281

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2005/000019

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1, 2, 8-16	as originally filed
3-7	filed with telefax on 03.04.2006

Claims, Numbers

1-12	filed with telefax on 03.04.2006

Drawings, Sheets

1/4-4/4	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2005/000019

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

IV

According to rule 13.1 PCT, an international application shall relate to one invention or to a group of inventions so linked as to form a single inventive concept.

The problem to be solved by invention 1 is considered to relate to the provision of alternative processes for the preparation of the optically pure ramipril(I), which is a known compound (cf e.g. US6407262B1)

The problem to be solved by invention 2 is considered to relate to the provision of a hydrated form of Ramipril (I) and process for the preparation of this form.

The above problems and their solutions are completely distinct.

The solution to invention 1 involves the crystallisation of optically impure Ramipril (I) from specified organic solvents, whilst invention 2 involves the provision of Ramipril(I) monohydrate.

The above problems and solutions are considered to be distinct and not to have a common inventive concept, since no special feature can be identified, which defines a contribution over the prior art.

V and VI

Reference is made to the following documents:

D1: US-B1-6 407 262 (WANG ZHI-XIAN ET AL) 18 June 2002 (2002-06-18)
D2: US-A-4 587 258 (GOLD ET AL) 6 May 1986 (1986-05-06)
D3: US-B1-6 541 635 (TIEN MONG-JONG ET AL) 1 April 2003 (2003-04-01)
D4: WO 2004/064809 A (SANDOZ GMBH; BHARATRAJAN, RAMASWAMI; ZEISL, ERICH; KOFLER, NIKLAUS; PA) 5 August 2004 (2004-08-05)
D5: US-A-5 061 722 (TEETZ ET AL) 29 October 1991 (1991-10-29)

Invention 1

Novelty

The specific solvents used in claim 1 for the optical purification of ramipril are not disclosed in D1 (cf claims 1-8 and examples of D1).

Inventive Step

The closest prior art is considered to be D1, in view of the fact that this discloses a process for the preparation of ramipril(I), using various organic solvents to obtain the desired optical isomer.

The skilled person would have tried alternative solvents to those disclosed in D1 for the qualitative recrystallisation of ramipril, such that the problem underlying the invention is considered to be the provision of a further crystallisation process for obtaining optically pure ramipril(I) having surprising effects compared to the processes of D1.

Table I demonstrates that using the claimed solvents, improved properties (bulk density and tap density are acheived. An inventive step can therefore be acknowledged.

Invention 2

D4 is only relevant for the examination of novelty and inventive step of claim 8,since the priority of the present application is not valid for these claims.

Novelty

None of the documents D1-D3 or D5 disclose hydrated forms of ramipril (I), such that claims 3-7,9-12 (priority valid) are novel vis-a vis these.

D4 refers in general on page 3, 4th paragraph to hydrates of ramipril, and does not refer to the preparation of a monohydrate form, such that also claim 8 is novel

Inventive Step

Claims 3-12

The closest prior art is considered to be D1-D3 or D5 (and where relevant D4).

D1-D3 and D5 disclose ramipril (I), but not the hydrated form.

The problem underlying claims 3-12 is considered to be the provision of a further form of ramipril (I) having a surprising effect compared to the closest prior art forms.

On page 9 of the description a comparison is made between the physical characteristics of the monohydrate (e.g. bulk density) of the invention compared to samples from D5.

These improved effects are considered to demonstrate an inventive step for claims 3-12.

The following may however have to be considered at the regional stage of examination.

The monohydrate formed in the processes of claims 7-11 is broader than the specific monohydrate of the product claims. Thus it my have to be considered whether it can be generally expected that all monohydrate forms would have the desired improved properties on which the inventiveness is based.

Certain Cited Documents

The priority of the present application is valid, for all claims apart from claim 8.

In the case that the priority is valid (all claims apart from claim 8) D4 does not constitute prior art within the meaning of Rule 64.1 (b).

It may be noted that the present claims are not anticipated by D4.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2 and D3 are not mentioned in the description, nor are these documents identified therein.

VIII

The claims should as far as possible not rely on the description for their meaning, therefore the chemical formula. Having regard for ramipril(I) in the claims, the chemical formula is given in the description.

C_6 alcohol, C_6 -C_8 aromatic hydrocarbon, C_3 -C_{10} ether, C_3 -C_6 ketone, C_2 -C_7 ester, C_1 to C_3 chlorinated compounds, and C_5 -C_{10} hydrocarbon solvents.

Although, the abovementioned method claims to give Ramipril(I) of more than 99% purity, suffers from the disadvantages of utilizing the solvents which are not recommended by Regulatory and Environmental bodies, since these solvents belong to the list of Class II solvents as categorized by International Conference on Harmonization (ICH). Moreover, many of these solvents have very low flash points which render their use, on commercial scale, hazardous.

There exists a need therefore, for a method for obtaining Ramipril(I) of high optical purity which overcomes the shortcomings associated with the prior art methods.

An object of the present invention is to provide the process of preparation of optically pure Ramipril(I) having optical purity of at least 99.9% by crystallisation of optically impure Ramipril consisting of a mixture of undesired diastereomers up to 20%, from a solvent or a mixture of solvents selected from a group consisting of nitroalkanes, acetals and ethers.

It is another object of the present invention is to provide a novel hydrated form of Ramipril(I) which has, a distinct X-ray (powder) diffraction pattern, a distinct DSC thermogram, a distinct thermogravimetric curve and a distinct IR spectrum, which is different from the reported form of Ramipril(I).

A further object of the present invention is to provide a novel monohydrate form of Ramipril(I) having bulk density in the range of 0.2 to 0.24 g/ml.

A further object of the present invention is to provide anhydrous form of Ramipril(I) comprising of drying Ramipril monohydrate obtained above at a temperature of about 40 °C under reduce pressure of 2 to 5 mm Hg, it gives anhydrous Ramipril(I) of high bulk density (0.3-0.35 g/ml).

A further object of the invention is to provide a process for the preparation of monohydrate of Ramipril(I) comprising of crystallizing optically pure Ramipril(I) from water.

A further object of the present invention is to provide anhydrous form of Ramipril(I) comprising of drying Ramipril monohydrate obtained above at a temperature of about 40 °C under reduce pressure of 2 to 5 mm Hg, it gives anhydrous Ramipril(I) of high bulk density (0.3-0.35 g/ml).

A further object of the invention is to provide a process for the preparation of monohydrate of Ramipril(I) comprising of crystallizing optically pure Ramipril(I) from water.

SUMMARY OF THE INVENTION

Thus the present invention relates to a process for purification of optically impure Ramipril to obtain (2S,3aS,6aS)-1-[(S)-2-[[(S)-1-(ethoxycarbonyl)-3-phenylpropyl]-amino] propanoyl] octahydro cyclopenta[b]pyrrole-2-carboxylic acid, viz. Ramipril(I) having optical purity of at least 99.9 %, which comprises crystallizing optically impure Ramipril from an organic solvent selected from nitromethane, dimethoxymethane, diethoxymethane, and 2,2, -dimethoxy propane and mixtures thereof

The Ramipril(I) obtained through crystallization from the abovementioned solvents or a mixture thereof has very high optical purity i.e., it is free of other stereoisomers. Further, the product so obtained exhibits improved physical characteristics such as bulk density, thermal stability, better dissolution profile, etc. which renders it highly suitable for formulation into a suitable dosage form.

For the purpose of this specification optically pure Ramipril(I) is defined as Ramipril(I) having optical purity of at least 99.9%, which is having all the chiral carbon centres in the S-configuration and, is free from other undesired stereoisomers.

Accordingly, the present invention provides the process of preparation of optically pure Ramipril(I) having optical purity of at least 99.9%.

According to a preferred aspect the process for the preparation of optically pure Ramipril(I) having optical purity of at least 99.9% comprises crystallisation of optically impure Ramipril consisting of a mixture of undesired diastereomers up to 20%, from a solvent or a mixture of solvents selected from a group consisting of nitroalkanes, acetals and ethers.

Although when the optically impure Ramipril is crystallised from highly polar hydroxyl solvents it does not form any hydrates even with methanol nor it forms any solvates with solvent having high dipole moment such nitromethane, but it has been surprisingly found that impure Ramipril when crystallized from a mixture of water and water immicible solvents, a 1:1 solvate i.e. hydrate form of Ramipril(I) having all the carbons in the S-configuration, crystallised out leaving all the other stereoisomer behind in the solvent i.e. in the filtrate.

It is further surprisingly found that if the Ramipril(I) monohydrate obtained above is dried at a temperature of 40 °C under reduced pressure of 2 to 5 mm Hg, it gives anhydrous Ramipril(I) of high bulk density (0.3-0.35 g/ml)

In another aspect of the present invention there is provided a novel hydrated form of Ramipril(I) which has, a distinct X-ray (powder) diffraction pattern, a distinct DSC thermogram, a distinct thermogravimetric curve and a distinct IR spectrum, which is different from the reported form of Ramipril(I) .

According to a further aspect of the present invention there is provided a novel monohydrate form of Ramipril(I) having bulk density in the range of 0.2 to 0.24 g/ml.

In a further aspect, the present invention relates to a novel monohydrate form of Ramipril(I) and a process for preparation thereof comprising of crystallizing optically impure Ramipril from a mixture of water and water-immiscible solvents.

DETAILED DESCRIPTION OF THE DRAWINGS

Fig. 1a : The X-ray (Powder) diffraction pattern of the Ramipril hydrate obtained by the process of the present invention.

Fig. 1b: The IR Spectrum of the Ramipril hydrate obtained by the process of the present invention.

Fig. 1c: The DSC thermogram of the Ramipril hydrate obtained by the process of the present invention.

Fig. 1d: The TGA thermogram of the Ramipril hydrate obtained by the process of the present invention.

Fig. 2: The crystal structure of the Ramipril hydrate obtained by the process of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel method for obtaining Ramipril(I) in high optical purity, free of other stereoisomers, and having high bulk density, comprising of crystallizing optically impure Ramipril from a solvent or a mixture thereof.

The solvents are selected from a group consisting of nitroalkanes such as nitromethane and acetals, such as dimethoxymethane, diethoxymethane and 2,2-dimethoxy propane.

Typically, one of the above solvents or a mixture thereof is added to the optically impure Ramipril consisting of a mixture of undesired diastereomers up to 20% and the solution is stirred at 20-25 °C for 20-50 minutes, cooled to –10 to 10 °C and stirred again for 2-5 hrs. The solid product which separates out is filtered, washed with cold solvent and dried. The product so obtained has an optical purity of 99.9%.

The compact, crystalline Ramipril(I), so obtained, has a bulk density in the range from 0.22 to 0.24 g/ml which is the most suitable for pharmaceutical preparations.

The bulk density is an economically, commercially, and functionally important property. High bulk density of the active pharmaceutical compound facilitates compression of tablets and filling of capsules. Additionally, very good flowability can be obtained with high-bulk-density powders. Moreover, when shipping powders over long distances a high bulk density results in reducing the shipping volume. A high bulk density compound also saves packing material and storage capacity.

A comparison of the bulk density (BD), tapped density (TD) and melting point of Ramipril(I) obtained by using various solvents of present invention and of prior-art process is summarised in Table-I hereinbelow.

Table – I Comparison of the physical properties of Rampril obtained by the Prior Art methods and the method of the present invention

Method	Solvent	B.D. (g/ml)	T.D. (g/ml)	M.P. (°C)
Prior art	Ethanol-diisopropyl ether	0.08-0.1	0.13-0.15	105.6-106.4
	Ethanol-diethyl ether	0.09-0.12	0.15-0.17	105.5-107
Present invention	Diethoxymethane	0.22-0.24	0.32-0.37	105.6-107.2
	2,2-Dimethoxypropane	0.1-0.13	0.14-0.18	104.7-105.7
	Nitromethane	0.12-0.14	0.15-0.17	104.8-105.4

Table II depicts the stability data of Ramipril(I) crystallized by diethoxymethane which shows that the Ramipril(I) obtained through crystallization from the abovementioned solvents or a mixture thereof exhibits acceptable physical characteristics such as stability.

CLAIMS

1. A process for purification of optically impure Ramipril to obtain Ramipril(I) having optical purity of at least 99.9 %, which comprises crystallizing optically impure Ramipril from an organic solvent selected from nitromethane, dimethoxymethane, diethoxymethane, and 2,2, -dimethoxy propane and mixtures thereof.

2. The process as claimed in claim 1 wherein the organic solvent is diethoxymethane.

3. A monohydrate of Ramipril(I), characterized by the following X-ray powder diffraction pattern

Diffraction angle 2θ	Relative Intensity (%)
8.7	16
9.2	3
9.4	3
9.7	3
11.2	81
11.6	33
12.2	66
14.54	96
15.7	70
18.0	51
19.7	81
24.5	49
24.8	30

4. The Ramipril(I) monohydrate as claimed in claim 3 having an X-ray diffractogram, or substantially the same X-ray diffractogram, as set out in Figure 1a.

5. The Ramipril(I) monohydrate as claimed in claim 3 having DSC thermogram as described in Fig. 1c.

6. The Ramipril(I) monohydrate as claimed in claim 3 having TGA thermogram as described in Fig. 1d.

7. A process for preparation of Ramipril(I) monohydrate comprising of crystallizing optically impure Ramipril from a mixture of water and water-immiscible solvents.

8. The process claimed in claim 7wherein the ratio of water-immiscible solvent to water is in the range from 2 to 98% w/w.

9. The process as claimed in claim 8 wherein the said water-immiscible solvent is selected from an aliphatic ester, an acetal, a hydrocarbon or a mixture thereof.

10. The process as claimed in claim 8 wherein the said water-immiscible solvent is selected from diisopropyl ether, diethoxymethane, 2,2-dimethoxy propane, cyclohexane, methyl isobutyl ketone and ethyl acetate or a mixture thereof.

11. A process for preparation of Ramipril(I) monohydrate comprising of crystallizing optically pure Ramipril(I) from water.

12. A pharmaceutical composition comprising an effective ACE inhibitory amount of Ramipril(I) monohydrate as claimed in any preceding claims, together with one or more pharmaceutically acceptable carriers, diluents or excipients thereof.